Comparison of Ribavirin plasma concentrations in HIV-monoinfected and HIV/HCV-coinfected patients with or without concomitant HAART

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Objective

Patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) taking highly active antiretroviral therapy (HAART) are on higher risk to be hospitalized or to die because of liver-related problems than of HIV-related illnesses. Therefore, treatment of HCV in HIV-patients is important but difficult, especially due to a higher risk of toxicities and pharmacological interactions with HAART. Standard therapy for HCV is pegylated interferon and RBV even in HIV patients. However, the response rates in HCV/HCV-coinfected patients are worse than in HCV-monoinfected ones and various reasons therefore have been described so far. Ribavirin (RBV) plasma concentration (PC) might play a crucial role not only in deteriorating drug addiction side effects like hemolytic anemia but also in effectiveness of treatment and early virological response. PC of RBV has been described to be an independent predictor of virological response. \[1,2\]

Methods

Plasma samples from outpatients with Hepatitis C receiving antiviral therapy with Ribavirin and pegylated Interferon have been collected and PC of RBV has been measured at various timeframes. Retrospective analysis was performed to determine the correlation between PC and HIV-coinfection as well as with a concomitant medication with HAART. A high performance liquid chromatography (HPLC) was established to determine PC of RBV after solid phase extraction \[3\]. For protein precipitation, plasma samples have been frozen and processed as following: Solid phase extraction (SPE) technique using a BAKERBOND spe 12g-vacuum extraction unit with Bond Elut LRC-PBA, 100mg. The HPLC-system consists of a HPLC pump with a 168 photodiode-detector, a 508 automated sample provider and the 32 Karat software for Windows NT for controlling, and data analysis. An aliquot of 50µl was injected into the HPLC column and the 250 mm x 2 mm ID column was packed with ReproSil-PUR C18-AQ 250 x 2 mm ID with a bead size of 5µm 20mM KH\textsubscript{2}PO\textsubscript{4}-buffer:Acetonitril gradient grade 99:1 (v/v) at pH 4.5 with a flow of 0.2ml/min was used as an eluent. The detection wavelength was set at 230nm. Standard curves were obtained in a concentration range from 50 – 6000 ng/ml (0.21 – 24.6 µmol/L) with linearity over the whole concentration range. Retention times: ISTD (3-Methylcytidin Methosulfat) 11,075 and RBV 7,383 min. An example of a HPLC is shown in figure 1.

Results

A total of 178 samples of 78 patients has been collected. We received up to 7 samples per patient, working with the mean PC of each patient. Only PC determined during steady state, i.e. after 4 weeks of treatment and at least 4 hours after drug intake, have been included in this study. 67 patients (136 samples) had HCV only and 11 patients (42 samples) have been coinfected with HIV and HCV. 7 of the HCV/HCV-coinfected patients were treated only against HCV (20 samples) and 4 patients (22 samples) received concomitant HAART, respectively (figure 2).

An interindividually wide spectrum of RBV PC has been measured. The plasma trough level for RBV in all samples was 1702 ± 582.5 ng/ml. In patients with HCV only the trough level was 1724 ± 590 ng/ml, in HIV/HCV-coinfected patients without HAART the trough level was 1721 ± 623 ng/ml. For patients coinfected with HCV and HIV receiving concomitant HAART a inferior trough level of 1302 ± 225 ng/ml was detected (figure 3).

The daily RBV dose in all patients ranged from 300 to 1200 mg with a mean dose of 975 ± 225 mg per day. In HCV-monoinfected the daily dose was 991 ± 226 mg, in HIV/HCV-coinfected 829 ± 214 mg and in patients with concomitant HAART 958 ± 142 mg per day, respectively. (figure 4).

Conclusion

We could show a correlation between HAART and reduced PC of RBV. As the daily RBV dose in the population with HAART was similar to the other patients, this might not explain the lower PC. No difference has been determined between PC in HCV-monoinfected and in HIV/HCV-coinfected patients without concomitant HAART. Thus, the HIV-infection itself seems to have no influence on the PC.

Several parameters influencing PC of RBV have not been taken into account, i.e. e. concomitant medication other than HAART, age, sex, side effects, virologic response etc. To improve efficacy of treatment of HCV especially in HIV/HCV-coinfected patients on the one hand and to reduce side effects on the other, further investigation has to follow. This study will be continued and extended.

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